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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,349	04/15/2005	Catherine J. Pachuk	NUCL-019/01US 306512-2117	9095

58249 7590 01/03/2008

COOLEY GODWARD KRONISH LLP
ATTN: Patent Group
Suite 1100
777 - 6th Street, NW
WASHINGTON, DC 20001

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
01/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,349	PACHUK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-174* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *108-174* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 108-168, 173 and 174 drawn to an expression construct encoding an RNA complex comprising a first strand and a second strand that are capable of hybridizing to each other under physiological conditions to form a double-stranded region, said double-stranded region comprising one or more mismatched regions that separate said double-stranded region into two or more double-stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases and wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide sequence, or an RNA molecule comprising one or more stem-loop structures comprising a double-stranded stem region and a single-stranded loop region each separated by a single-stranded spacer region, wherein the double-stranded stem region of at least one stem-loop structure comprises one or more mismatched regions, wherein said one or more mismatched regions separates said double stranded stem region into two or more double stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases and wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide sequence.

Group 2, claim(s) 169 and 170, drawn to a method for generating a ribonucleic acid complex comprising a first strand and a second strand that are capable of hybridizing to each other under physiological conditions to form a double-stranded region, said double-stranded region comprising one or more mismatched regions that separate said double-stranded region into two or more double-stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases and wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide sequence, or an RNA molecule comprising one or more stem-loop structures comprising a double-stranded stem region and a single-stranded loop region each separated by a single-stranded spacer region,

wherein the double-stranded stem region of at least one stem-loop structure comprises one or more mismatched regions, wherein said one or more mismatched regions separates said double stranded stem region into two or more double stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases and wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide sequence wherein said method comprises contacting an expression construct encoding said RNA complex or RNA molecule with cell-free components or by administering the expression construct to a cell or a mammal, under conditions that allow expression of said RNA complex or RNA molecule.

Group 3, claim(s) 171-172, drawn to a method for reducing or inhibiting the expression of a target gene in a cell, said method comprising administering to a subject in need thereof a nucleic acid molecule that comprises or that encodes a ribonucleic acid (RNA) complex comprising a first strand and a second strand that is capable of hybridizing to each other or that has hybridized to each other under physiological conditions to form a first double-stranded region, said first double-stranded region comprising one or more mismatched regions that separate said first double-stranded region into two or more double-stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases and wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide sequence, or an RNA molecule comprising one or more stem-loop structures comprising a double-stranded stem region and a single-stranded loop region each separated by a single-stranded spacer region, wherein the double-stranded stem region of at least one stem-loop structure comprises one or more mismatched regions, wherein said one or more mismatched regions separates said double stranded stem region into two or more double stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases and wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide sequence, wherein said administering occurs under conditions that allow cleavage of said expressed or administered RNA complex or RNA molecule by a single-stranded RNA-specific ribonuclease (RNase) to liberate said double-stranded segments of said RNA complex or RNA molecule, wherein said liberated double-stranded segments from said RNA complex or RNA molecule are capable of reducing or inhibiting the expression of a target polynucleotide sequence, relative to the expression of said target polynucleotide sequence in a cell lacking said RNA complex or RNA molecule.

The inventions listed as Groups 1-3 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons. The technical feature linking the claimed inventions was anticipated by the prior art, and so cannot be

a special technical feature under PCT Rule 13.2. Zeng et al (Mol. Cell 9: 1327-1333, June, 2002) taught expression vectors encoding miRNAs. See entire document. Zeng taught expression vectors comprising a CMV immediate early promoter operably linked to sequences encoding a variety of miRNAs including mir-30 precursor, mir-30-nxt precursor, mir-30-PTB, and mir-30-TAg. These miRNAs were molecules that formed RNA complexes comprising a first strand and second strand that hybridized to each other, were separated by a loop, and contained at least one mismatch in the hybridizing region. One strand of the hybridizing region had homology to a target polynucleotide sequence from either a cellular mRNAs (mir-30 target mRNAs, nxt mRNA, or PTB mRNA) or a pathogen mRNA (SV40 T antigen mRNA). See paragraph bridging pages 1327 and 1328; Fig. 1 on page 1328; paragraph bridging pages 1328 and 1329; Fig. 2 on page 1328; Fig. 3 on page 1329; Fig. 4 on page 1330, and supporting text. Zeng also taught methods of making the constructs or molecules by contacting cells with the expression constructs, and methods of inhibiting the expression of the target genes in subject cells. Accordingly, Zeng anticipates each of independent claims 108, 169, and 171, and there can be not unity of invention among the restricted groups.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. Applicant is required to elect for examination a single expression construct, and to specify its structure with respect to the following characteristics:

1. The number of target polynucleotides with which the double stranded segments have "substantial identity", and the number and nature of target sequences targeted. For example instant claims read on:

expression constructs wherein a portion of one of said double-stranded segments of said RNA complex or said RNA molecule has substantial sequence identity to one target polynucleotide sequence;

expression constructs wherein said RNA complex or RNA molecule comprises two or more double stranded segments having substantial sequence identity to the same target polynucleotide sequence (e.g. instant claims 117 and 121);

expression constructs wherein said RNA complex or RNA molecule comprises two or more double stranded segments having substantial sequence identity to different target polynucleotide sequences within the same target polynucleotide sequence (claims 118, 119, and 121);

expression constructs wherein said RNA complex or RNA molecule comprises two or more double stranded segments having substantial sequence identity to different target polynucleotide sequences within different target polynucleotide sequences (claims 118, 120, 121); and

expression constructs wherein said RNA complex or RNA molecule comprises at least two mismatched regions that separate said double-stranded region of said RNA complex or at least one double-stranded stem region of said RNA molecule into at least three double-stranded segments. (claim 122).

2. The presence or absence at the 5' or 3' end of said first or second strand of a specified number of stem-loop structures comprising a double-stranded stem region and a single-stranded loop region each separated by a single-stranded spacer region, wherein the double-stranded stem region of at least one stem-loop structure comprises a specified number of mismatched regions, wherein said one or more mismatched regions separates said double stranded stem region into a specified number of double stranded segments, wherein said mismatched regions are susceptible to cleavage by single-strand ribonucleases. If this feature is present, Applicant is required to specify the precise number of each feature above indicated by the phrase "a specified number of".

3. The presence or absence in the expression construct of a plurality of said RNA molecules covalently linked in a 5' to 3' orientation. (e.g. claims 140 and 141).

4. The presence or absence in the construct of a gene encoding an RNA polymerase, e.g. claim 160.

5. Whether or not the nature of the target polynucleotide sequence is limited, and if so, to what it is limited, e.g. a host gene associated with a cancer (claims142-144, 151-153), a host gene associated with a dsRNA-mediated toxicity (claims142-144,151-153), a host gene associated with an autosomal dominant disorder (claims142-145, 151-153, a host gene associated with an autosomal recessive disorder (claims142-145, 151-153), a host gene encoding a receptor that mediates infection of a cell by a pathogen (claims142-145, 151-153 and 149), a reporter gene (claim 142), a gene of a bacterium (claims 142 and 146-151), a gene of a yeast or fungus (claims 142 and 146-151), a gene of a protozoan or parasite, (claims 142 and 146-151).

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims

subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed as indicated above.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the reasons given above, i.e. several of them are anticipated by the prior art. See Zeng above who taught expression vectors comprising a CMV immediate early promoter operably linked to sequences encoding a variety of miRNAs. Zeng taught miRNAs that formed RNA complexes comprising a first strand and second strand that hybridized to each other, were separated by a loop, and contained at least one mismatch in the hybridizing region. One strand of the hybridizing region had homology to a target polynucleotide sequence from either a cellular mRNA (mir-30 target mRNAs, nxt mRNA, or PTB mRNA) or a pathogen mRNA (SV40 T antigen mRNA). See paragraph bridging pages 1327 and 1328; Fig. 1 on page 1328; paragraph bridging pages 1328 and 1329; Fig. 2 on page 1328; Fig. 3 on page 1329; Fig. 4 on page 1330, and supporting text.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not

distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central

fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635